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(71) Applicant: BAXTER INTERNATIONAL INC. [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US).

(72) Inventors: PEJAVER, Satish, K.; 49 Huntley Way, Bridgewater, NJ 08807 (US). MOTHERAM, Rajeshwar; 909 Cloister Road, Apt. D, Wilmington, DE 19809 (US).

(74) Agents: NICHOLS, Jeffrey, C. et al.; Baxter Healthcare Corporation, One Baxter Parkway, Deerfield, IL 60015 (US).

(54) Title: PROPOFOL COMPOSITIONS CONTAINING PRESERVATIVE ADDITIVES

(57) Abstract

Formulations of intravenous anesthetic propofol emulsions are provided which produce a stable emulsion and simultaneously inhibit microbial growth thereby providing protection against accidental microbial contamination during long-term IV infusions through the use of pentetic acid or its derivatives.

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PROPOFOL COMPOSITIONS CONTAINING PRESERVATIVE ADDITIVES

This application claims the benefit of U.S. Provisional Application No. 60/128,428 filed April 5, 1999.

Field of the Invention

This invention generally relates to improved pharmaceutical formulations of the intravenous anesthetic propofol with enhanced microbial characteristics. More particularly, this invention relates to an improved propofol emulsion formulation which is bacteriostatic and in certain forms bactericidal with the use of trace amounts of an antimicrobial additive.

Background of the Invention

Propofol (2,6 diisopropylphenol) is a hydrophobic, water-insoluble oil which is widely used as an anesthetic agent via IV administration. Propofol is generally incorporated in a vegetable oil emulsion to enable intravenous administration.

Sterile pharmaceutical compositions of propofol and their use in inducing anesthesia are generally described in U.S. Patents Nos. 4,056,635; 4,452,817 and 4,798,846, all to Glen and James. The propofol/soybean oil emulsion has gained widespread use for induction and/or maintenance of anesthesia, for maintenance of monitored anesthesia care and for sedation in the Intensive Care Unit (ICU). It is advantageous in that it possesses both a rapid onset anesthesia and a short recovery time.

One problem associated with the compositions described in the before mentioned patents is the risk of bacterial contamination primarily due to the high soybean oil content, and lack of anti-microbial preservatives.

It has been shown that the propofol emulsion formulated without preservatives will grow bacteria. The oil content, combined with a lack of anti-microbial additives, present a risk of bacterial contamination (Arduino et al., 1991, Sosis & Braverman, 1993; PDR, 1995).

To address the problem of bacterial contamination of propofol emulsions, additional formulations of propofol have been developed. One such formulation is described in U. S. Patent no. 5,731,356. It is believed that the commercially available

product described in that patent is marketed under the tradename DIPRIVAN and comprises a sterile, pyrogen-free oil-in-water emulsion containing 1% (w/v) propofol in 10% (w/v) soybean oil dispersed in water and stabilized by 1.2% (w/v) lecithin phospholipids. The product also includes a commonly used preservative, EDTA to provide a claimed benefit of less than one log increase in growth of certain gram-positive and gram-negative bacteria over a twenty-four period. A second formulation, described in U. S. Patent No. 5,637,625, is an oil-free formulation in which, in one described form, the propofol is in a 6.8% wt/wt concentration and dispersed in water as micro-droplets with a diameter generally less than 1 micron, having a phospholipid or monoglyceride outer covering. However, it appears that upon administration this formulation may increase site irritation to an unacceptable level.

Since emulsion is a biphasic system, addition of known preservatives at their usual levels, may lower the amount of preservative in the aqueous phase due to partitioning between the phases, to a degree dependent on lipophilic properties of preservative and hence, may not provide the anti microbial effect being sought. In addition, inclusion of known preservatives can cause physical instability of emulsion system.

Since propofol emulsion is used for induction and maintenance of general anesthesia, and for sedation, considerable volumes may be administered, resulting in administration of significant amounts of added preservative, posing a safety concern. Consequently the concentration of preservative should preferably be as low as possible. Thus extensive research is needed for incorporation of even known preservatives in an emulsion system in general and propofol emulsion in particular.

A combination of safety, efficacy and compatibility with emulsion limits the use of most known preservatives. Hence we investigated the use of other excipients for anti microbial effect. It was found that DPTA (diethylene triamine penta acetic acid), which is an ion sequestering agent that has found wide use in radio pharmaceuticals, unexpectedly showed the desired anti microbial effect, since DTPA was not shown to have broad spectrum anti microbial properties previously. Furthermore, anti-microbial effect of DTPA was found at very low concentrations which would minimize concerns for safety and instability of emulsion.

The problems described above are substantially reduced if not eliminated by an improved propofol formulation provided in accordance with the present invention.

Summary of the Invention

The preferred embodiment of the present invention provides a propofol formulation, preferably an emulsion having anti-microbial properties with the use of amounts of an additive at very low concentrations. An important feature of the propofol formulation of the present invention is a reduced risk of bacterial growth after site contamination, which may occur, in a medical care giving setting

Detailed Description of the Preferred Embodiment of the Invention

Accordingly, the present invention provides a sterile pharmaceutical composition for parenteral administration which, in the preferred embodiment, comprises an emulsion in which propofol is dissolved in a water-immiscible solvent, preferably soybean oil and which further comprises a trace amount of an antimicrobial additive such that there is a deterrence of significant growth of microorganisms for at least 24 hours, following adventitious, extrinsic contamination. An emulsion meaning a distinct, two-phase system that is in equilibrium.

Generally, the composition of the present invention preferably contains a microdroplet, approximately 200 nanometers in mean diameter, comprised of propofol, dissolved in an oil or other solvent, surrounded by a surfactant, and suspended in a pharmaceutical acceptable injectable carrier and including a trace amount of an anti-microbial additive.

A wide range of water-immiscible solvents can be used in the compositions of the present invention. Typically, the water-immiscible solvent is a vegetable oil, for example soybean, safflower, cottonseed, corn, sunflower, arachis, castor or olive oil. Preferably, the vegetable oil is soybean oil. Alternatively, the water-immiscible solvent is an ester of a medium or long-chain fatty acid, for example, a mono-, di-, or triglyceride; or is a chemically modified or manufactured material such as ethyl oleate, isopropyl myristate, isopropyl palmirate, a glycerol ester, polyoxyl hydrogenated castor oil. In a further alternative the water-immiscible solvent may be a marine oil, for example cod liver or another fish-derived oil. Suitable solvents also include fractionated oils, for example, fractionated coconut oil or modified soy bean

oil. Furthermore, the compositions of the present invention may comprise a mixture of two or more of the above water-immiscible solvents.

Suitable surfactants include synthetic non-ionic surfactants, for example ethoxylated ethers and esters polypropylene-polyethylene block co-polymers, and phospholipids for example, naturally-occurring phospholipids such as egg and soya phospolipids and modified or artificially manipulated phospholipids (for example prepared by physical fractionation and/or chromatography), or mixtures thereof. Preferred surfactants are egg phospholipids, such as lecithin.

The composition of the present invention may be made isotonic with blood by the incorporation of a suitable tonicity modifier, for example glycerin.

The composition of the pharmaceutically acceptable injectable carrier is preferably a pyrogen free water, or Water for Injection U. S. P.

In the preferred embodiment of the present invention, to the propofol emulsion described generally above, a concentrated aqueous solution of an anti-microbial additive is added to yield a trace amount of such an additive in the final concentration. More particularly pentetic acid or its derivatives thereof are added to the propofol emulsion to provide a concentration ranging from 0.0025% - 0.01%. Pentetic acid includes, diethylene triamine penta acetic acid ("DPTA") and derivatives of pentetetic acid include calcium trisodium pentetate and pentetate penta sodium.

DPTA is an ion sequestering agent and has found wide use as an imaging agent in radio pharmaceuticals. Additionally, pentetic acid is included in pharmaceutical compositions as an anti oxidant for stabilization purposes. but it is not believed that DPTA has been used as an anti-microbial additive in an emulsion similar to a propofol emulsion.

Generally to formulate the present invention, propofol (1-2%) is dissolved in Soybean oil (5-10%) constituting the oil phase. Glycerin (2.25%) and Lecithin (1.2%) are added to Water for Injection at 60 ± 10 °C and mixed until a uniform dispersion is formed, constituting the aqueous phase. The oil phase is added to aqueous phase while stirring to form the primary emulsion. The primary emulsion is then recirculated through a homogenizer under high pressure, until the globule size of the emulsion is approximately 200 nm. DTPA free acid, DTPA calcium tri sodium

salt or DTPA penta sodium salt are then added to arrive at a concentration of 0.0025% - 0.1%, more suitably 0.0025% - 0.01%, most suitably 0.005% - 0.01%.

The pH of the final emulsion is adjusted with sodium hydroxide, filtered and filled under nitrogen and steam sterilized. The appearance of the formulation is a white opaque liquid. The mean globule size is approximately 200 nm. The pH of finished product is between 7 - 8.5. The emulsions were stable after single and double autoclaving.

The compositions of the present invention are useful as anesthetics, which includes sedation and induction and maintenance of general anesthesia. Accordingly, the present invention provides a method of producing anesthesia in a warm-blooded animal, including humans, comprising administering parenterally a sterile aqueous pharmaceutical composition which comprises an oil-in-water emulsion in which propofol, in a water-immiscible solvent, is emulsified with water and stabilized by means of a surfactant.

Dosage levels of propofol for producing general anesthesia, both induction (for example about 2.0-2.5 mg/kg for an adult) and maintenance (for example about 4-12 mg/kg/hr), and for producing a sedative effect (for example 0.3-4.5 mg/kg/hr), may be derived from the substantial body of literature on propofol. Furthermore, the anesthetist and/or physician would modify the dose to achieve the desired effect in any particular patient, in accordance with normal skill in the art.

The anti-microbial effects of propofol compositions including trace amounts of pentetic acid or its derivatives is illustrated in the following tables which detail the microbial growth upon the addition of suspensions of standard USP test organisms (Pseudomonas aeruginosa ATCC 9027, Staphylococcus aureus ATCC 6538, Escherichia coli ATCC 8739, and Candida albicans ATCC 10231) to test formulations at an initial inoculum concentration of about 100 colony forming units (cfu) per mL, which approximates touch contamination. The test formulations included the listed concentrations (expressed in percent wt/v) of DTPA free acid, DTPA calcium tri sodium salt or DTPA penta sodium salt and a similar propofol emulsion without any DPTA or other anti-microbial additive. The test formulations containing bacteria were then incubated at 30°C - 35°C and those containing Candida

were incubated at 20°C - 25°C and counted for viable colonies after 24 and 48 hours in duplicate.

Table 1

	S. aureus (log cfu/mL)			P. aeruginosa (log cfu/mL)		
Time (hr.)	0	24	48	0	24	48
DTPA 0.0025%	1.76	1.91	2.04	1.74	2.04	4.11
DTPA 0.005%	1.84	2.00	1.91	1.85	1.72	2.78
DTPA 0.0075%	1.74	1.89	1.89	1.78	1.69	2.98
DTPA 0.01%	1.74	1.93	1.80	1.74	1.74	2.63
0.0075% DTPA Ca 3Na	1.76	2.00	2.04	1.77	3.00	4.78
0.0075% DTPA 5 Na	1.76	1.96	1.79	1.79	1.71	2.74
P. control	1.73	3.00	3.12	1.82	3.12	6.31

Table 2

	E. coli (log cfu/mL)			C. albicans (log cfu/mL)		
Time (hr.)	0	24	48	0	24	48
DTPA 0.0025%	2.11	1.36	0.30	1.89	2.68	2.93
DTPA 0.005%	2.15	1.28	0.30	1.87	2.59	2.82
DTPA 0.0075%	2.13	1.42	0.81	1.98	2.74	2.88
DTPA 0.01%	2.08	1.39	0.74	2.03	2.68	2.91
0.0075% DTPA Ca 3Na	2.11	1.68	1.04	2.15	2.97	3.11
0.0075% DTPA 5 Na	2.18	0.85	0.00	2.18	2.65	2.85
P. control	2.15	5.59	7.83	1.99	3.52	5.16

In particular, as set forth in the tables the preferred embodiments produce anti-microbial effects approximating those described in embodiments described in U.S. Patent No. 5,637,625 incorporated by specific reference herein.

From the foregoing description, it will be apparent that the formulation of the present invention has a number of advantages, some of which have been described above, and others which are inherent in the invention. Also, modifications can be made to the formulation without departing from the teachings.

Claims

What is claimed is:

1. An oil-in-water propofol emulsion which comprises water and globules containing propofol and a water immiscible agent surrounded by a surfactant and further comprising an amount of one of pentetic acid and derivatives of pentetic acid sufficient to show anti-microbial effect.

2. The emulsion of Claim 1, wherein the pentetic acid includes diethylene triamine penta acetic acid and derivatives of pentetic acid include calcium trisodium pentetate and pentetate penta sodium.

3. The emulsion of Claim 2, wherein the emulsion comprises diethylene triamine penta acetic acid.

4. A sterile, pyrogen free, injectable pharmaceutical composition consisting essentially of a minor amount of the emulsion of claim 1, and a major amount of a pharmaceutically acceptable injectable vehicle.

5. The injectable pharmaceutical composition of Claim 4, in which the pharmaceutical composition is isotonic.

6. An oil-in-water propofol emulsion which comprises water and globules containing propofol and a water immiscible agent surrounded by a surfactant and further comprising an antimicrobial agent, the agent including amount of one of pentetic acid and derivatives of pentetic acid in a concentration ranging from 0.0025%-0.1%.

7. The oil-in-water emulsion of claim 6 wherein the agent comprises diethylene triamine penta acetic acid.

8. A method of preparing an oil-in-water emulsion pharmaceutical composition suitable for parenteral administration of an comprising:

dissolving hydrophobic propofol in a water-immiscible solvent, constituting an oil phase, mixing a surfactant and a tonicity modifier with Water for Injection, constituting an aqueous phase, mixing the oil phase with the aqueous phase to form a primary emulsion, recirculating the primary phase through a homogenizer to produce microdroplets of about 200 nm and adding an anti-microbial agent comprising of pentetic acid and derivatives of pentetic acid to form a final emulsion, adjusting the pH of the final emulsion using sodium hydroxide to produce a pH of 7 - 8.5, and steam sterilizing the emulsion.

9. A method according to Claim 8, wherein the antimicrobial agent comprises diethylene triamine penta acetic acid.

10. A method according to Claim 8, wherein the agent is added in a concentration ranging from 0.0025%-0.1%.

11. A method according to Claim 10, wherein the agent is added in a concentration ranging from 0.005%-0.01%.

INTERNATIONAL SEARCH REPORT

Ins tional Application No
PCT/US 00/08379

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/107 A61K47/18 A61K31/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 6 028 108 A (GEORGE) 22 February 2000 (2000-02-22) the whole document	1-11

☐ Further documents are listed in the continuation of box C.

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6028108 A	22-02-2000	WO 0023050 A	27-04-2000